The Examiner asserts that "the combination of references clearly suggests that the substituted prolactin mimics phosphorylation, and that phosphorylation results in an antagonistic molecule, therefore, one of ordinary skill in the art would reasonably conclude that substitution to mimic phosphorylation would likely generate an antagonistic molecule, absent evidence to the contrary."

There is No Motivation to Combine Maciejewski and Walker and Maciejewski Teaches Away from Such a Combination

Applicant respectfully submits that there is no motivation to combine the Maciejewski and Walker references and that Maciejewski teaches away from such a combination. As discussed in more detail below, Maciejewski teaches that serine 90 is the critical phosphorylated residue in prolactin and that **substitution of other phosphorylated residues does not mimic the biological effect of phosphorylated prolactin**. Further, Maciejewski fails to teach or suggest that serine 179 is phosphorylated at all, much less that it is a critical residue in the biological activity of phosphorylated prolactin.

One of Skill in the Art Would Not Believe that Serine 179 and Serine 90 are Equivalent

At the time the present application was filed, there was disagreement in the art about the major site of phosphorylation in prolactin and its biological significance. As indicated in Walker, some evidence suggested that serine 179 or its species equivalent (177) was the major site of phosphorylation, while other reports indicated that serine 90 was the critical residue (page 196, second and third columns). For example, Wang et al. (J. Biol. Chem. 271:2462-2469 (1996), of record) concluded from their analysis of rat prolactin that "the primary site of PRL phosphorylation is serine 177. Phosphorylation at this site has a major effect on biological activity causing the phosphorylated PRL to become an antagonist to the non-phosphorylated hormone." (page 2649, first column, last paragraph). In contrast, Brooks et al. (Mol. Cell. Endocrin. 99:301-305 (1994), of record) found that serine 90 in bovine prolactin was the major phosphorylation site and was responsible for biological activity in the Nb2 bioassay. One of skill in the art would recognize that these positions are inconsistent and that both residues could not

be the major site of phosphorylation. Thus, one of skill in the art would not expect results obtained with serine 90 to be applicable to serine 177/179. Moreover, without the benefit of the present disclosure, one of skill in the art would not have been able to identify one residue over the other as being involved in the antagonistic activity of phosphorylated prolactin. As the Examiner is aware, the present disclosure can not be used in the rejection to provide motivation to combine references.

Maciejewski Teaches that Only Substitution of Serine 90 Mimics Phosphorylation

The Examiner states that Maciejewski "teach that substituted prolactin mimics phosphorylation, therefore, one of ordinary skill in the art would reasonably expect that a substituted prolactin, which mimics phosphorylation, would possess the antagonistic activity as taught by Walker." Applicant disagrees that Maciejewski teaches that substituted prolactin mimics phosphorylation. However, even if it did so, **Maciejewski teaches that only substitution of serine 90 mimics phosphorylation** because that serine is the critical residue for the biological activity. Maciejewski states that their results "confirm our interpretation of previous sequence and stoichiometric studies that demonstrated serine 90 to be the most frequently phosphorylated and probably responsible for the reduced biological activity of the phosphorylated hormone." (page 27664, column 1, first full paragraph). Maciejewski does not teach or suggest that substitution of any other residue can mimic the activity of phosphorylated prolactin.

Maciejewski Teaches that Substitution of Other Serine Residues does Not Mimic Phosphorylation

While bovine prolactin contains a serine at position 179, Maciejewski does not identify this as a phosphorylated residue and does not suggest that it may be important to the activity of the phosphorylated protein. Maciejewski did identify two phosphorylated residues in addition to serine 90, but found that **mutation of the two other phosphorylated serine residues did not mimic the biological activity of phosphorylated prolactin** (page 27664, second column, fourth full paragraph). Further, Maciejewski argues for the importance of serine 90 by specifically

stating that this particular residue is conserved in prolactins, as well as in other hormones (page 27663, first column, lines 5-7). Thus, Maciejewski teaches that **only substitution of serine 90 mimics the biological activity of phosphorylated prolactin and teaches away from generalizing their findings to any other phosphorylated residues.**

The Examiner has stated that "Walker teaches that this serine [179] is important for biological activity and phosphorylation creates an antagonist for prolactin" (paper no. 16, page 4, first full paragraph). However, Maciejewski teaches that serine at position 90 is the **only critical residue and the only residue whose substitution can mimic phosphorylation**. Thus, one of skill in the art would not believe that mutation of serine 179 could mimic the biological effects of phosphorylated prolactin and would not be motivated to combine the teachings of Maciejewski with the teachings of Walker. In addition, the commercial success of the present invention points to its unobviousness. As a result, Applicant respectfully requests that this rejection be withdrawn.

Conclusion

For the reasons presented above, Applicant respectfully submits that all pending claims are in condition for allowance, and an early action to that effect is respectfully solicited. If any issues remain, Applicant requests that the Examiner contact Applicant's counsel at the number listed below to schedule an interview in order to resolve such issues promptly.

Respectfully submitted,

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